Wiley
European Journal of Cancer Care
Volume 2025, Article ID 5824491, 6 pages
https://doi.org/10.1155/2025/5824491

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Research Article

Elevated CA15-3 Levels in Myeloid Disorders: Clinicopathological Correlation

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Received 29 September 2023; Revised 5 April 2024; Accepted 7 October 2024

Academic Editor: Sourav Panja

Background: Serum tumor markers are beneficial to patients with advanced cancer because they help in early diagnosis, determining prognosis, predicting response to certain medications, and monitoring therapy. The prognostic value of cancer antigen 15-3 (CA15-3) serum-level changes in breast cancer is very well established. The main cause behind the elevation of CA 15-3 is metastatic breast carcinoma. In this study, we will run a record review to study comprehensively the clinical association between chronic myeloid disorders and CA15-3 elevation.
Method: In this retrospective study, we run CA15-3 on 106 patients with different myeloid disorders diagnosed between 2008 and 2021 from several tertiary care centers in Saudi Arabia, Jeddah, majority of which (38 cases) were diagnosed with chronic myeloid leukemia (35.8%). Others had essential thrombocytosis (22.6%), chronic myeloproliferative neoplasm (20.8%), myelofibrosis (7.5%), acute myeloid leukemia (4.7%), myelodysplastic syndrome (4.7%), and polycythemia vera (3.8%).
Result: An increase in CA15-3 was seen in 50% of all cases. In particular, polycythemia vera showed an elevation in 100% of the cases (4 out of 4). Second in expressivity is myelodysplastic syndrome (80%, 4 out of 5 cases). Close in value is myelofibrosis (75%, 6 out of 8 cases). The least association is noted between CA15-3 and essential thrombocytosis (16.7%, 4 out of 24 cases).
Conclusion: When CA15-3 levels are considered during the time of myeloid disorder diagnosis, it shows an independent predictive value. More research is needed to determine the utility of these serum biomarkers in myeloid disorders decision-making. This is a thorough case series of chronic myeloid disorders inclusive of all myeloproliferative neoplasms besides myelodysplastic syndrome describing the association with CA15-3.

1. Introduction

Both normal and malignant cells release tumor markers. When cancer is present, the levels are substantially greater. It is a low cost, minimally intrusive diagnostic method. Yet, for it to be a viable technique of diagnosis, it must be able to detect tumors in their earliest stages [1]. To determine whether further care modifications should be made, tumor markers are also useful in assessing cancer prognosis following chemotherapy and radiotherapy.

CA15-3 is a useful serum tumor marker for breast cancer. The incidence of breast cancer has been progressively growing throughout the years. When a patient treatment fails, their quality of life and their chances of survival are severely reduced [2]. To enhance the prognosis, it is vital to establish accurate indicators that may be used to guide treatment decisions. Breast cancer metastasis detection, prognosis assessment, treatment response prediction, and disease recurrence rely heavily on CA15-3 serum tumor marker. As a result, CA15-3 has been the foremost broadly utilized serum tumor marker within the clinical fields for a long time [3].

CA15-3 is one of several chemicals known as tumor markers, which can rise as a cancer develops and regress as a tumor responds to treatment [4]. CA15-3 is a breast tissue antigen that is frequently measured. Other benign and malignant conditions according to certain research studies can

also express elevation in CA15-3. The CA15-3 levels can be also increased in chronic active liver disease, liver cirrhosis, sarcoidosis, hypothyroidism, and megaloblastic anemia [5].

CA15-3 antigens are Y-shaped proteins that serve as a cell's unique "signature" in the body. Despite the fact that the CA15-3 antigen does not cause cancer, it can develop in number as cancer cells that quickly grow. The extent of CA15-3 antigens is directly proportional with the tumor growth rate. As a sign of disease progression (metastases to bone or liver), CA15-3 can be elevated as well. CA15-3 antigens are elevated in the majority of metastatic breast carcinoma cases, in contrast to early stages where it has low incidence of elevation [6]. For these reasons, CA15-3 can be used to monitor breast cancer that has metastasized to other regions of the body at stage 4. In addition, the oncologist can analyze the effectiveness of a cancer treatment by monitoring CA15-3 readings on a regular basis.

The term "chronic myeloproliferative neoplasm" describes a group of hematological malignancies marked by the overproduction of mature myeloid cells in the bone marrow and their release into the blood. These disorders fall under the wider category of myeloproliferative disorders (MPDs), which include conditions such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Chronic myeloproliferative neoplasms share common characteristics, such as clonal hematopoiesis, where they originate from a single progenitor cell that has acquired mutations leading to uncontrolled growth. There is also an overproduction of one or more blood cell types, including red blood cells, white blood cells, or platelets. These disorders have the potential to progress into more aggressive diseases like acute myeloid leukemia (AML). Patients may exhibit a range of symptoms due to the overproduction of cells, such as an increased risk of thrombosis or bleeding, and common complications include splenomegaly due to extramedullary hematopoiesis.

The manuscript "Elevated CA15-3 Levels in Myeloid Disorders: Clinicopathological Correlation" investigates the link between chronic myeloid disorders and elevated levels of the serum tumor marker CA15-3, which is traditionally associated with breast cancer. By incorporating various myeloid disorders such as chronic myeloproliferative neoplasm into their study, the authors aim to assess the potential of CA15-3 as a diagnostic or prognostic biomarker in a wider clinical setting beyond breast cancer. The manuscript emphasizes that chronic myeloproliferative neoplasm is part of a spectrum of diseases caused by dysregulated myeloid cell production and that the examination of CA15-3 levels represents an inquiry into the pathological commonalities between these seemingly unrelated diseases.

To our knowledge, there is no thorough case series inclusive of all myeloid disorders, particularly myelodysplastic syndrome outlining the association with CA15-3. Thus, the objective of this study was to investigate this association.

2. Method

Alinity i CA15-3 is a two-step chemiluminescent microparticle immunoassay from Abbott, designed to detect DF3 antigens in serum. Reactivity with two monoclonal antibodies is used to measure CA15-3 (generated against human milk fat globule membrane antigens). In this study, CA15-3 is conducted in 106 serum samples obtained from patients with different myeloid disorders at multiple referral centers. CA15-3 is flagged as high when it rises above 25 U/mL. The patients were diagnosed with bone marrow aspirate and trephine biopsy along with applicable flow cytometry molecular markers (i.e., JAK2 and BCR-ABL were utilized). This retrospective record review of clinical records was conducted after obtaining the unit of biomedical ethics—research committee's approval.

In this retrospective study, we classified patients with myeloid disorders based on the WHO classification and diagnostic criteria for myeloproliferative neoplasms [7]. Patients who had clear-cut diagnostic criteria for polycythemia vera, myelofibrosis, and essential thrombocytosis were labeled according to their respective diagnoses. The diagnostic criteria for these conditions were followed to ensure accurate classification.

However, it is important to note that some patients presented with clinical features that did not definitively indicate a specific myeloproliferative neoplasm. These cases had a more ambiguous presentation and did not fulfill the criteria for a precise diagnosis of polycythemia vera, myelofibrosis, or essential thrombocytosis. To include these cases that exhibited features consistent with a myeloproliferative neoplasm but did not meet the strict criteria for a specific subtype, we classified them under the broader category of chronic myeloproliferative neoplasms.

This approach allowed us to encompass a comprehensive range of myeloid disorders, including both the well-defined subtypes and cases with ambiguous presentations. By including patients under the chronic myeloproliferative neoplasms category, we ensured the inclusion of cases that exhibited characteristics of myeloproliferative neoplasms but did not fit into a specific subtype based on the established diagnostic criteria.

3. Result

A total of 53 out of 105 patients (50.47%) were noted to have elevated CA15-3. The aforementioned patients are breast cancer free. A diagnosis of polycythemia vera was found to be the mostly correlated (100% of the patients). Closer values are depicted by myelodysplastic syndrome (80%) and myelofibrosis (75%). On the other hand, essential thrombocytosis shows the least percentage of relation (17.4%) (Table 1). Patients with elevated CA15-3 were 24 females and 29 males with an average age of 52 (range: 13–91) (Table 2). Despite the fact that breast cancer is more common in females, the association between CA15-3 and gender is not statistically significant (p value: 0.20).

In this study, we examined the range of CA15-3 value of each diagnosis and genders. Box plots represent the interquartile range, with the median indicated by the line inside the box. Whiskers extend to the minimum and maximum values, and any points beyond the whiskers are considered outliers (Figure 1).

Table 1: Relation between myeloid disorders and elevated CA15-3.

Subtype	Elevated CA15-3	Total, N (%)	High (%)
Polycythemia vera	4	4 (3.8%)	100
Myelodysplastic syndrome	4	5 (4.8%)	80
Myelofibrosis	6	8 (7.6%)	75
Chronic myeloproliferative neoplasm	13	22 (21%)	59.1
Chronic myeloid leukemia	21	38 (36.2%)	55.3
Acute myeloid leukemia	1	5 (4.8%)	20
Essential thrombocytosis	4	23 (21.9%)	17.4
Total	53	105 (100%)	50.47

Table 2: Distribution of patients with elevated CA15-3.

Gender	High CA15-3	Total, *n* (%)	High (%)
Female	24	54 (51.4%)	44.4
Male	29	51 (48.6%)	56.9
Total	53	105 (100%)	50.47

Myelofibrosis and chronic MPDs share a symmetric distribution similar to that of polycythemia vera. However, the highest median is observed in polycythemia vera. Both chronic myeloid leukemia and myelodysplastic syndrome exhibit a positively skewed distribution. On the other hand, AML and primary thrombocytosis demonstrate a negatively skewed distribution have the lowest medians. Outliers are present in chronic myeloid leukemia, chronic MPDs, and primary thrombocytosis. In analysis of CA15-3 levels by diagnosis, the 95% confidence interval for the mean ranged from 30.09 to 40.09 (one-way ANOVA).

The post hoc test using the Games–Howell method indicated that there were significant differences in CA15-3 levels between several hematological disorders. AML had a significant lower CA15-3 levels than myelofibrosis (mean difference = −25.578, 95% CI [−50.53, −0.62], $p = 0.043$) and chronic myeloid leukemia (mean difference = −25.217, 95% CI [−47.49, −2.95], $p = 0.019$). Moreover, chronic myeloid leukemia showed higher CA15-3 levels compared with primary thrombocytosis (mean difference = −20.029, 95% CI [0.50, 41.55], $p = 0.041$). These differences highlight distinct patterns of CA15-3 expression in specific hematological diseases, which may provide insights into pathophysiology or disease progression.

The median test score for males is slightly higher than that for females. Whiskers indicate a slightly wider spread in the male group, suggesting greater variability in test results among males. There are a few outliers in both the female and male box plots, with the same highest value (Figure 2). When comparing the levels of CA15-3 by gender, the 95% confidence interval for the mean difference ranged from −8.775 to 12.129 (Independent *t*-test).

The scatter plot was constructed to investigate the potential relationship between the age and CA15-3 levels. However, the points on the scatter plot appear to be scattered widely with, indicating a weak association (Figure 3). For this relationship, the 95% confidence interval for the mean difference ranged from −14.818 to −1.131 with a non-significant p value ($p = 0.806$).

4. Discussion

The CA15-3 is an immunoassay that quantitatively measures DF3 antigen. CA15-3 test parameters utilize the DF3 and 115D8 monoclonal antibodies, prepared against metastatic breast carcinoma and milk-fat globule membranes, respectively [8–13]. This explains that the frequent elevation of CA 15-3 is encountered in patients with breast cancer. Researchers have recommended that the CA15-3 assay may be useful for treatment-response follow-up as the values' variability is directly correlated with disease progression [8, 14–19]. Further publications stated that increasing CA15-3 levels are detected in patients at risk for recurrent breast malignancy [15–17, 20].

Several benign breast and liver diseases demonstrated a rise in CA15-3. In addition, nonmammary malignancies including lung, colon, pancreas, liver, ovary, cervix, and endometrium showed increased levels of CA15-3 as well. Most normal individuals have CA15-3 values within the normal limit [14, 21, 22].

CA15-3 is an epitope of MUC1, a large transmembrane glycoprotein translated from *MUC1* gene [23]. Yin and colleagues investigated the effect of blocking MUC1 oncoprotein cytoplasmic tail to prompt terminal differentiation of chronic myelogenous leukemia cells [24]. Subsequently, Rughetti et al. described that CA15-3 (soluble MUC1) levels were higher in Ph-negative myeloproliferative chronic disorders patients, specifically more evident in polycythemia vera patients and in female cases [25]. In this study, our findings are concordant with the polycythemia vera association. In addition, it also highlights the association between CA15-3 and myelodysplastic syndrome, which may introduce CA15-3 as a potential targetable antigen for further studies.

The value of this marker can assist in diagnostic and prognostication. Yet, future studies are warranted in this direction.

The inclusion of AML in the study is justified on the grounds that it is a myeloid disorder, and the study aims to comprehensively investigate the clinical association between various myeloid disorders and CA15-3 elevation. By examining the CA15-3 levels across a spectrum of myeloid disorders, the researchers aim to determine whether this marker can have predictive value or serve as a diagnostic or prognostic tool in conditions other than breast cancer.

The importance of this study lies in its potential to expand the clinical utility of CA15-3 and to uncover new

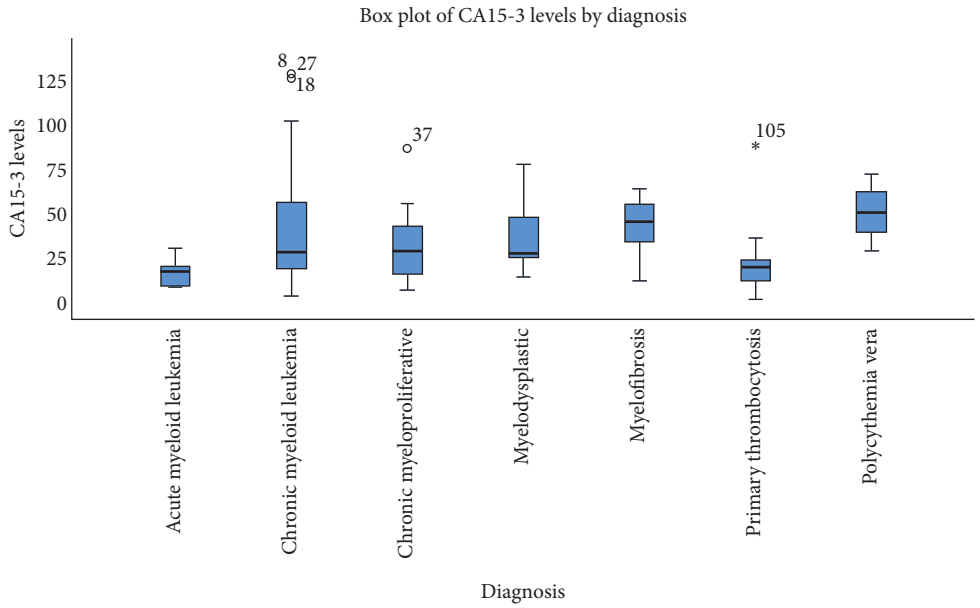

Figure 1: Box plot of CA15-3 results by diagnosis.

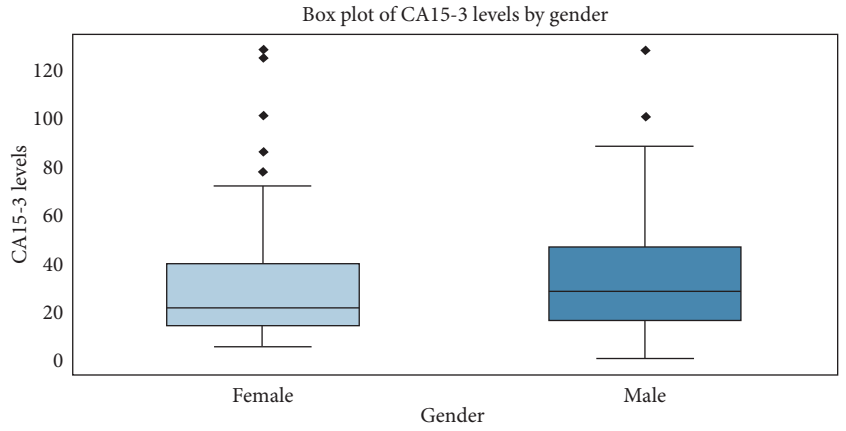

Figure 2: Box plot of CA15-3 results by gender.

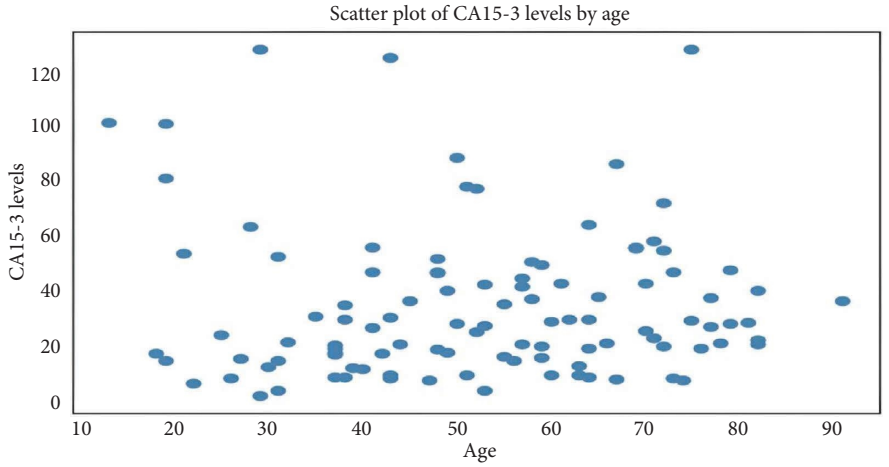

Figure 3: Scatter plot of age versus CA15-3 levels.

facets of its behavior in hematological malignancies. This could lead to improved diagnostic strategies or the discovery of new treatment targets. The findings suggest that CA15-3 may not be exclusively indicative of breast cancer but may also be elevated in certain myeloid disorders, which warrants further investigation. The study calls for additional research to confirm these findings and to explore the mechanisms behind CA15-3 elevation in myeloid malignancies, including AML.

5. Conclusion

Breast cancer is tracked by the CA15-3 biomarker. The CA15-3 antigen is a protein that cancer cells release into the bloodstream. Although the CA15-3 antigen is intimately linked to breast cancer, it is also linked to other malignant and noncancerous disorders. To our knowledge, this is the first comprehensive case series of myeloid disorders inclusive of myelodysplastic syndrome, which showed this particular association. The rise in serum CA15-3 levels is associated with a variety of myeloid disorders, especially polycythemia vera, myelodysplastic syndrome, and myelofibrosis. Our work, we feel, will help shed light on potential hematological malignancies research efforts in the future.

Data Availability Statement

All data generated or analyzed during this study are included within the article (Tables 1 and 2).

Ethics Statement

This study was approved by the Committee of Biomedical Ethics at King Abdulaziz University, Jeddah, KSA (no. 362-21). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants involved in the study. Minor participants' informed consent has been obtained from a parent and/or legal guardian.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Both authors designed the research, performed the research, contributed vital new reagents or analytical tools, analyzed the data, and wrote the paper.

Funding

The authors received no specific funding for this work.

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